Title

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Journal

Endocrinology, Diabetes & Metabolism Case Reports, 2024(3)

ISSN

2052-0573

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Publication Date

2024-07-01

DOI

10.1530/EDM-24-0031

Peer reviewed

Endocrinology, Diabetes & Metabolism CASE REPORTS

EDM Case Reports (2024) **2024** e240031
https://doi.org/10.1530/EDM-24-0031

Received 9 March 2024
Accepted 22 July 2024
Version of Record Published 16 August 2024

Transient synovitis associated with leuprolide depot (Lupron)

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Summary

A 6.6-year-old female presented to endocrinology with precocious puberty for evaluation and management. Workup was initiated, and a diagnosis of central precocious puberty was confirmed. A decision was made to initiate pubertal blockade using gonadotropin-releasing hormone agonist (GnRHa) therapy with depot leuprolide acetate injections every 3 months. The patient received the first depot leuprolide acetate injection in the right ventrogluteal area. Six hours following the injection, the patient was reported to be inconsolable in pain, which was localized to the right hip site of the earlier injection and associated with a refusal to ambulate. The pain and discomfort continued to progress over the next 24 h despite an alternating regimen of Tylenol and ibuprofen prompting admission to the emergency department. Vital signs demonstrated a low-grade fever and elevated C-reactive protein. An ultrasound of the right hip demonstrated fluid accumulation within the joint. Over the next week, the patient was unable to walk independently and required assistance for activities of daily living. By 2 weeks after the injection, the pain began to remit, and the patient resumed activities of daily living. Following consultation with allergy, a decision was made to continue GnRHa suppressive therapy with an alternative analog (Triptodur). The patient tolerated subsequent treatment without reaction.

Learning points

- Although gonadotropin-releasing hormone agonists (GnRHa) have a generally good safety profile, there is a history of both local and systemic hypersensitivity reactions associated with their use.
- Despite the long-acting formulation of depot leuprolide acetate, the systemic reaction in this case appears to be self-limited.
- Discontinuation of therapy or a change to an alternative formulation of GnRHa analog should be considered based on the need for therapy versus the potential risk of rechallenge.

Background

Gonadotropin-releasing hormone (GnRH) agonists are routinely used in the treatment of prostate cancer, breast cancer, endometriosis, and uterine leiomyomas (1). Leuprolide acetate was the first GnRH agonist to enter clinical development, being first approved in 1985 for daily use in prostate cancer patients (2). In pediatrics, GnRH agonists have become the standard of care in the management of central precocious puberty (CPP) (3). Mechanistically, pubertal initiation is signaled by

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EDM Case Reports (2024) **2024** e240031
https://doi.org/10.1530/EDM-24-0031

the onset of pulsatile GnRH secretion with subsequent activation of pituitary gonadotrophs. Resultant increases in gonadal steroid production lead to the characteristic changes of puberty. Pulsatility of the GnRH signal is required to activate pituitary gonadotrophs. Selective suppression of the hypothalamic–pituitary–gonadal axis can be achieved using long-acting (non-pulsatile) GnRH agonists (GnRHa) (4). GnRHa therapies have been Food and Drug Administration (FDA) approved for use in CPP since 1993 (5). Depot leuprolide acetate was the first FDA-approved GnRHa for the treatment of CPP with a later release of a number of formulations differing in their duration of activity. Six-month subcutaneous leuprolide acetate was the most recent FDA approved GnRHa for use in CPP. All GnRHa analogs have a D-amino acid substitution in the sixth position of the sequence. Some analogs, including leuprorelin, also have a substitution at the tenth position in the sequence (6). GnRH agonists have a favorable safety profile, with the most frequent adverse effects reported as injection site pain and headache (7). Rare adverse effects have also been reported, including effects on the nervous system, skin, gastrointestinal tract, cardiovascular system, and local and systemic hypersensitivity reactions (7).

Case presentation

A 6.6-year-old female with a history of high-functioning autism presented to endocrinology for premature thelarche and concern for precocious puberty. The onset of breast development and tenderness began approximately 1 month prior and had been progressive. In association with this, the mother has also noted new onset vaginal discharge. Other findings include body odor with the use of deodorant over the past year. A recent growth spurt was denied. No change was reported in her baseline of inconsistent behavior. Phytoestrogen exposure was endorsed with daily household use of a lavender infuser and scented floor cleaner. Growth records demonstrated consistent growth at the 80th percentile since about 2 years of age. Labs obtained 2 weeks prior to our visit showed a total serum estrogen level of 144.7 pg/mL (follicular phase: 90–590 pg/mL) using a radioimmunoassay for determination of estradiol within the range of normal for a reproductively mature female. Gonadotropins were obtained using more sensitive third-generation immunochemiluminometric assays with pediatric reference ranges (8). Luteinizing hormone pediatric (LHp) was 0.17–mIU/mL (≤0.15 mIU/mL Tanner 1) and follicle-stimulating hormone pediatric was 5.14 mIU/mL (0.72–5.33 mIU/mL).

Past medical history is significant for autism without significant developmental delay and a remote history of genu valgum which resolved. Family history is positive for early pubertal growth in the father, who reached his final height by the end of middle school. Maternal menarche was on time at 12 years of age.

On physical examination, height is at the 82nd percentile and BMI is at the 33rd percentile. Tanner's staging was consistent with stage 3 breast and stage 2 pubic hair development. Vaginal examination showed immature labia minora, slight pallor of the vaginal mucosa, and white discharge.

Based on the above history, a diagnosis of CPP was suspected, with additional labs, imaging, and diagnostic testing requested.

Investigation

Labs obtained upon presentation to endocrinology demonstrate normal thyroid function. Bone age was 7 years and 10 months, while chronological age is 6 years and 7 months (S.D. 10 months). GnRH stimulation testing using 500 µg subcutaneous leuprolide acetate was performed without adverse effects. Results demonstrated a 1-h LHp of 5.11 mIU/mL (<5 mIU/mL) and a 24-h ultrasensitive estradiol of 169 pg/mL (<50 pg/mL), confirming a diagnosis of CPP (9, 10). No intracranial abnormalities were identified on subsequent brain MRI with pituitary cuts, confirming an idiopathic origin of CPP. The family elected to suppress puberty using gonadotropin-releasing hormone agonist (GnRHa) therapy. Depot leuprolide acetate (30 mg) every 3 months (12 weeks) was initiated.

Treatment

Two and a half months after presentation and about a month after GnRH stimulation testing, the patient received the first 30 mg depot leuprolide acetate injection in the outpatient clinic. The injection to the right ventrogluteal area resulted in vigorous resistance and required active restraint as she kicked, writhed, and fought the RN administering the leuprolide acetate dose. Following the injection, the patient, although upset, was not in pain and was ambulatory at discharge from the clinic. However, 6 hours later, the mother notified the on-call doctor that the patient was then inconsolable in pain and refusing to walk. The pain was identified as localized to the right hip, the site of the earlier leuprolide acetate injection. The mother was advised to apply warm compresses to the affected area and to begin an alternating regimen of Tylenol and ibuprofen. Over the next 24 h, the pain worsened, and the mother was directed to take the patient to the emergency department (ED) for evaluation.

In the ED, the patient was in pain and refusing to ambulate or bear weight. Vital signs demonstrated a low-grade fever of 100.6°F (38.1°C). On examination, she held her right hip in adduction and flexion, with severe pain elicited upon any movement. No swelling or pain was evident in the right knee or ankle, which retained full range of motion. The right hip injection site remained visible in the right ventrogluteal area and was without redness or swelling. Labs showed an elevation of C-reactive protein (CRP) at 2.1 mg/dL (0–0.99 mg/dL) and a normal complete blood count and differential.

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https://doi.org/10.1530/EDM-24-0031

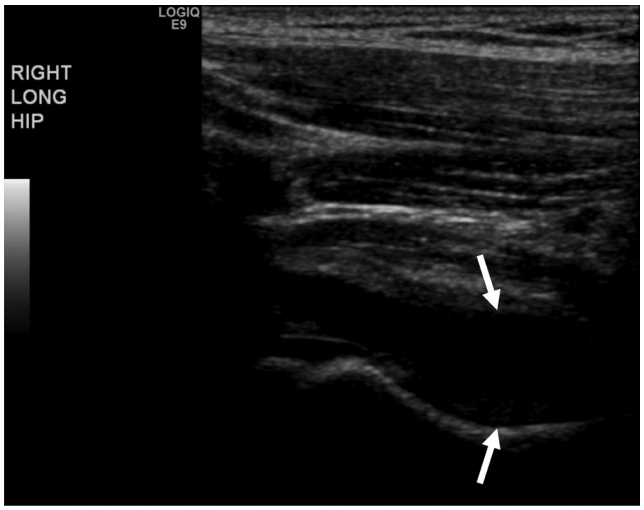

Figure 1

Ultrasound images of the right hip.

Blood culture was subsequently negative for growth at 72 h. Orthopedics was consulted and recommended ultrasound imaging of the hips. Images demonstrated an abnormal increase in joint fluid on the right without evidence of hematoma or joint trauma (Fig. 1). Based on examination and imaging findings, a diagnosis of right hip transient synovitis (TS) was made. The patient was given i.v. Toradol to address pain, which improved significantly shortly thereafter. A referral was placed for outpatient follow-up with orthopedics.

Over the next week, the patient was bedridden and initially required assistance for activities of daily living. With time, her clinical course improved, and by the 10th-day, post-injection, she was able to ambulate independently, although slowly and with an antalgic gait (Fig. 2).

Outcome and follow-up

About one and a half months after her adverse reaction to the leuprolide acetate injection, she was seen by orthopedics. Physical evaluation and imaging were consistent with complete resolution of hip pain and joint effusion with discharge from further follow-up. Two and a half months after the initial leuprolide acetate injection and prior to the scheduled repeat injection, the patient was seen in consultation with allergy/immunology to address the cause of the reaction and the likelihood of a recurrent reaction if rechallenged. Findings were felt to be most consistent with TS. Allergy testing was not recommended due to the absence of established protocols, but the family was advised to switch to an alternative GnRHa analog with a 1-h period of post-injection observation. The patient subsequently received 22.5 mg i.m. Triptodur without recurrence of the pain event. She has remained on Triptodur every 6 months (24 weeks) without recurrent adverse events.

Discussion

We report the first case of TS in association with GnRHa therapy. TS is an acute, nonspecific inflammation of the synovial membrane that typically presents as unilateral limb disuse and can be associated with joint effusion, elevation of inflammatory markers, and low-grade fever (11). This condition can be distinguished from septic arthritis based on the patient not meeting the Kocher criteria (12). The patient we report presented with severe pain localized to the right hip, refusal to bear weight, and an effusion of the underlying joint. Potential causes of this presentation would include generalized processes such as serum sickness and systemic allergy or localized processes such as joint trauma, intra-articular injection, TS, and septic arthritis. In this case, the patient's findings of fever and elevated CRP could be suggestive of a serum sickness-like generalized reaction, which may have been blunted by the scheduled administration of non-steroidal anti-inflammatory drugs (NSAIDs). However, the isolated nature of her complaints to the right hip as well as the absence of symptom generalization to a polyarticular reaction favors a localized process. The absence of skin manifestations, hypotension, shortness of breath, nausea, vomiting, diarrhea, and dizziness disfavors a systemic allergic reaction. An initial consideration for her findings was musculoskeletal injury due to the patient's vigorous resistance to the injection. This explanation, however, was not supported by physical examination findings in the emergency room, as there was no evidence of a

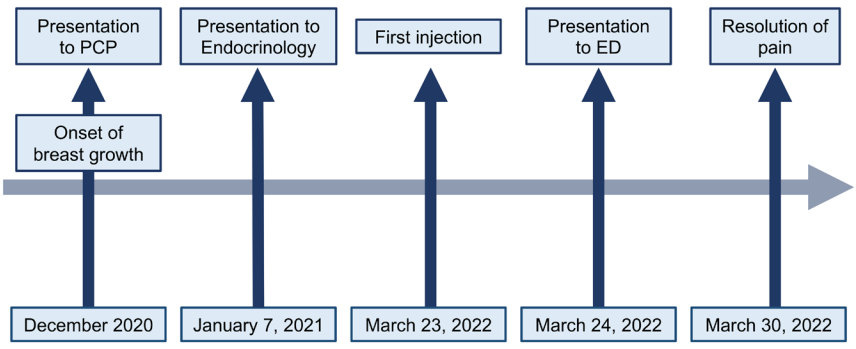

Figure 2

Timeline of patient course.

EDM Case Reports (2024) **2024** e240031
https://doi.org/10.1530/EDM-24-0031

pulled or strained muscle, and subsequent x-rays of the pelvis did not demonstrate a fracture.

Importantly, her findings could reflect either a local reaction to leuprolide acetate or an inadvertent direct intra-articular injection. Although we cannot rule out either of these as the cause of her findings, the following observations make these conclusions less likely. First, with regard to the possibility of a local reaction, there was no palpable pain, warmth, swelling, induration, bruising, or rash on examination at any time following the injection. Regarding the possibility of an inadvertent direct intra-articular injection, on review of the ultrasound findings and the location of the injection, it was the opinion of the radiologist that the needle was of insufficient length (1.5") to reach the joint capsule. Additionally, given the vigorous resistance by the patient at the time of the injection, if the joint was penetrated by the needle, one would expect some evidence of joint trauma, such as a hematoma, which was not evident on ultrasound. However, one cannot rule out lesser degrees of joint trauma as the cause of her findings. Given the absence of a definitive cause for her findings, a diagnosis of TS is considered.

There are many reports of adverse events to GnRHa therapy, ranging from mild localized reactions to severe systemic reactions. Local, self-limiting adverse reactions occur in 10–15% of patients, with the most reported being injection site redness, pain, and induration. Sterile abscesses have also been reported but with less frequency than other forms of localized reactions (0.3–3%) (13). Systemic hypersensitivity reactions are still less common and include urticaria, serum sickness, fixed drug reactions, and anaphylaxis (14). GnRH agonists are thought to result in localized release of histamine, which may underlie urticarial reactions (15). Serum sickness, a type III hypersensitivity reaction, may occur following a prior sensitizing exposure to GnRHa, such as the sensitization to depot GnRHa that occurs following a subcutaneous aqueous GnRHa stimulation test (16). Fixed drug reactions are rare, with a single report in which an injection of goserelin acetate resulted in intense erythema localized to a previously irradiated area (17). Lastly, a rare but serious systemic reaction is anaphylaxis, with an increasing number of cases reported (18, 19, 20, 21, 22). While most reports of anaphylaxis are isolated self-limited events, there is one report of recurrent anaphylaxis following the administration of a long-acting depot formulation of GnRHa (20).

According to the prescribing information for 3-month depot formulations of leuprolide acetate, musculoskeletal complaints are rare, and synovitis is not listed as an adverse event. Post-marketing reports from the manufacturer included tenosynovitis, but due to the voluntary nature of the reporting, the details of the adverse events, occurrence, and causality are unavailable. In one review of adverse reactions to GnRH agonist therapy, a patient was reported to have developed muscle stiffness in the leg immediately after injection. Pain was described as a spasm that lasted all day. Therapy was discontinued, and no other details were provided (23).

Clinically, the pain of TS is usually more severe than expected based on the appearance of the joint. Based on the patient's presentation and the exclusion of other causes, a diagnosis of TS appears to best fit the findings in this case. One limitation accompanying this novel adverse reaction is the lack of confirmatory allergy testing. Because of this, the identity of the allergen(s) cannot be determined with certainty. Potential causative factors would include both the GnRHa and vehicle constituents. Reactions to the latter have been previously reported (22, 24).

In summary, we present the first reported case of synovitis following depot leuprolide acetate injection. Findings include an acute pain reaction within 24 h of the injection, low-grade fever, elevated CRP, and fluid accumulation within the joint. The patient was treated with NSAIDs, and all clinical findings fully resolved within 2 weeks of onset. Therapy was continued with an alternative formulation of GnRHa without recurrence of symptoms. GnRHa therapy has been used without significant adverse effects for many years, but it is important to recognize that adverse effects may occur. Discontinuation of therapy or a change to an alternative formulation of analog should be considered based on the need for therapy versus the potential risk of rechallenge.

Declaration of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding statement
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Patient consent
Written informed consent for publication of their clinical details was obtained from the parent of the patient.

Author contribution statement
EAS and SAP wrote the manuscript. SAP was the physician responsible for the care of this patient.

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